The patient was a 61-year-old Vietnamese man who had undergone orthotopic liver transplantation on August 12, 1999, for end-stage liver disease secondary to hepatitis C. In the period following the transplantation, the patient experienced no acute cellular rejection. However, increasingly abnormal liver function test results led to a liver biopsy on October 31, 1999, which showed portal triaditis consistent with recurrent hepatitis C infection. The patient's course was stable until August 2000, when he complained of hiccups for the past week, excessive somnolence for the past 2 months, and a rash on the left side of his back for several days. In addition, he had polydipsia and polyuria in the preceding 2 weeks.

The patient's medical history was remarkable only for the chronic hepatitis C, which lead to his liver transplantation. Current medications included interferon alfa-2b recombinant, ribavirin, famotidine, and tacrolimus. He had no known drug allergies, and his only surgery was the liver transplantation. Results of the physical examination were unremarkable, but his blood glucose level was 696 mg/dL (38.6 mmol/L) (normal, 65–110 mg/dL [3.6–6.1 mmol/L]). He was admitted with diabetic ketoacidosis and was treated with intravenous fluid and insulin. The blood glucose level dropped to 8 mg/dL (0.4 mmol/L) within 2 days of treatment and became normal throughout the rest of the hospital stay.

For the refractory hiccups, the patient initially began treatment with chlorpromazine, but with no benefit. Other medications were tried but did not stop the hiccups. The patient then underwent an upper quadrant ultrasound, which showed multiple focal, hypoechoic nodules within the liver, one in the left lobe pressing directly on the diaphragm. These nodules were of varying size and had internal echoes. There was no ascites seen. A subsequent computed tomographic (CT) examination of the abdomen and pelvis also revealed these multiple low-density lesions within the liver (Figure 1). In addition, the spleen and a single portacaval node also showed similar lesions. A percutaneous CT-directed needle biopsy of the liver was performed, and the tissue showed a diffuse replacement of the liver parenchyma with large cells containing prominent nucleoli (Figure 2). The cells were in a sheetlike pattern with no lobulations. The cells were immunoreactive for CD45 (leukocyte common antigen) and CD20 (B-cell marker) (Figure 3). They were focally positive for Epstein-Barr virus (EBV) (Figure 4). The cells were negative for AE1/AE3 (low- and high-molecular-weight cytokeratins) and polyclonal carcinogenic embryonic antigen. A bone marrow biopsy was performed, the results of which showed a normocellular marrow with relative erythroid hyperplasia. Immunophenotyping of the bone marrow with flow cytometry did not find any unique cell population.

**What is your diagnosis?**
Pathologic Diagnosis: Large B-Cell Lymphoma
(Posttransplantation Lymphoproliferative Disorder)

Posttransplantation lymphoproliferative disorder (PTLD) was first described in 1968 following a 5-year study that showed an increased frequency of lymphoid tumors in immunosuppressed, organ transplant recipients. This disorder is a recognized, severe complication that arises in allograft recipients treated with immunosuppressive drugs. Histologically, PTLD is an abnormal growth of lymphoid cells, with most cases being of B-cell type. The term PTLD includes polyclonal, monoclonal, and multiple different monoclonal proliferations of lymphocytes. Whether polyclonal proliferations progress to monoclonal lymphomas has not been proven.

The incidence of PTLD varies with the organ transplanted and the nature and severity of the immunosuppressive regimen. In 1981, a study of renal transplant recipients with PTLD confirmed the presence of the EBV within most of these tumors. In 1995, Knowles et al. investigated PTLD lesions in 22 patients for alterations in bcl-1, bcl-2, c-myc, and H-, K-, and N-myc and for mutations involving the p53 gene. They found that alteration in the proto-oncogenes and p53 tumor suppressor gene may play an important role in the development and/or progression of PTLD. In a recent study, PTLD was seen in 6% of liver, 7% of heart, 5% of lung, 11% of heart and lung, and 4% of kidney allografts. In a different study, 8 (2%) of 428 patients who underwent allogeneic bone marrow transplantation developed PTLD. Of these, 5 patients had diffuse large B-cell lymphoma and 3 patients had polymorphous B-cell hyperplasia. As seen in these studies, PTLD is not a common complication but is one of the most frequent tumors among graft recipients.

A significant rise in the incidence of PTLD was seen after the introduction of cyclosporin A (cyclosporine) in the early 1980s. New potent immunosuppressants, such as anti-CD3, monoclonal OKT3, and FK506 (tacrolimus), and the recognition of this disease have subsequently led to increased numbers of cases with earlier presentation. Nalesnik et al. determined that the median time of onset of PTLD in patients initially immunosuppressed with cyclosporin A–containing regimens was 4.4 months after transplantation. They also confirmed the strong association of PTLD with EBV.

It is generally believed that the lymphocytes of PTLD are of host origin. Weissmann et al. studied PTLD in 11 patients receiving solid organ transplants at Massachusetts General Hospital. Using polymerase chain reaction to investigate genetic polymorphism on chromosomes 4, 13, and 19, they found 10 tumors to be of host origin and only 1 tumor of donor origin.

In summary, PTLD is a recognized, severe complication arising in allograft recipients treated with immunosuppressive drugs, especially cyclosporine. In addition, PTLD is an abnormal growth of lymphoid cells, most of B cell origin. Although PTLD is likely to be a progression from a polyclonal proliferation of lymphocytes (which may be reversed by discontinuing immunosuppressive therapy) to an uncontrolled monoclonal proliferation (lymphoma), that sequence has not been proven. There is a strong association of PTLD with EBV, with most PTLD lesions of host origin.

References